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**IDLE FREE CITY**  
CITY ORDINANCE 12.58.030



**TURN YOUR KEY. BE IDLE FREE!**

**2 MINUTE  
TIME LIMIT**

**IT'S OUR HEALTH, AND THE LAW.**

# Asthma

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Thursday, February 16, 2017

Utah Dept of Health Asthma Webinar

Director, Schmidt Chest Clinic, Intermountain Medical Center

# Learning objectives

1. Understand the treatment options for controlling asthma
2. Understand appropriate therapy for asthma exacerbations
3. Understand when advanced asthma therapies (new anti-IL-5 therapy) are indicated

38 yo M w/ asthma, poorly controlled, daily symptoms, using daily inhaled steroid and prn albuterol 3-5 times a day w/ frequent early am awakenings due to wheezing. Which do you recommend next?

1. Add LAMA (e.g. tiotropium)
2. Add ICS-LABA combination (e.g. budesonide-formoterol)
3. Add omeprazole
4. Start daily prednisone for a month and then wean as tolerated
5. Azithromycin x 5 days

# Trigger Avoidance

- Upper Respiratory tract Infections (viral “URI’s”)
- Irritants
  - Tobacco exposure/smoke exposure
  - **Outdoor Air pollution & Smog**
  - Indoor air pollution – ozone, candles, incense, “air fresheners”
  - Chemicals – cleaning chemicals, bleach, perfumes
  - Dust
  - Occupational sources
- Allergens
  - Dust
  - Cats/dogs/animals
  - Mold
- Co-morbidities/exacerbating factors
  - GERD
  - Allergic rhinitis
  - Obstructive Sleep Apnea

# Outdoor air pollution and asthma

**The Air Quality Index (AQI)** is a number for reporting how clean or unhealthy your air is every day.

You can find it on the Internet at  
AirNow.gov. It's also reported  
in local news sources:



## When AQI is:

## A person with asthma should:

1–50

**GOOD**



Enjoy usual  
outdoor activities



51–100

**MODERATE**



Consider reducing outdoor exercise —  
not as long, not as hard  
If you have symptoms,  
stay indoors

101–150

**UNHEALTHY**

for sensitive  
groups



Reduce  
or avoid  
outdoor  
exercise



Plan outdoor  
activities  
in the  
morning,  
when air  
quality is  
usually  
better



Keep your  
fast-acting  
inhaler nearby  
(such as  
albuterol)  
— and  
contact your  
doctor if  
you're using  
it often



Whenever  
possible,  
avoid  
outdoor air  
in places  
with a lot of  
traffic

Going  
even a few  
blocks away  
can help

151–200

**UNHEALTHY**

201–300

**VERY  
UNHEALTHY**

Avoid all  
outdoor  
exercise

# Trigger Avoidance

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- Irritants
  - Tobacco exposure/smoke exposure
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  - Dust
  - Occupational sources
- Allergens
  - Dust
  - Cats/dogs/animals
  - Mold
- Co-morbidities/exacerbating factors
  - **GastroEsophageal Reflux Disease (GERD)**
  - Allergic rhinitis
  - Obstructive Sleep Apnea

# Esomeprazole and asthma

- 412 subjects randomized for 24 week trial of PPI vs. placebo
- Primary outcome: poor asthma control based on daily diaries
- Secondary outcome: whether esophageal pH monitoring identifies subgroup that responds to PPI therapy for asthma
- Adults 18 and older with diagnosis of asthma and PFTs
  - Methacholine challenge test or bronchodilator response on spirometry
- On medium-high dose inhaled steroids or equivalent
- Poor asthma control – by questionnaires or prior exacerbations
- Minimal or no GERD symptoms



# Episodes of Poor Asthma Control and Component Events.

**Table 3.** Episodes of Poor Asthma Control and Component Events.\*

Variable	Placebo (N=193)	Esomeprazole (N=200)	Incidence- Rate Ratio, Esomeprazole vs. Placebo (95% CI)	Esomeprazole vs. Placebo†	P Value Gastroesophageal- Reflux Interaction‡
Asthma episodes, according to definition that did not include use of beta-agonists as a criterion					
No. of events	201	224			
No. of events/person-yr	2.3	2.5	1.1 (0.8–1.5)	0.66	0.93
Patients with ≥1 event (%)	42	42			
Exacerbation components					
≥30% drop in peak expiratory flow on 2 consecutive days					
No. of events	141	180			
No. of events/person-yr	1.7	2.1	1.2 (0.8–2.0)	0.35	0.99
Patients with ≥1 event (%)	26	28			
Urgent care visit					
No. of events	53	51			
No. of events/person-yr	0.6	0.6	0.9 (0.6–1.5)	0.79	0.44
Patients with ≥1 event (%)	17	18			
New use of oral corticosteroids					
No. of events	50	48			
No. of events/person-yr	0.6	0.5	0.9 (0.6–1.3)	0.62	0.85
Patients with ≥1 event (%)	24	21			

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Asthma episodes, according to definition that included increased use of beta-agonists					
No. of events	367	383			
No. of events/person-yr	4.4	4.3	1.0 (0.8–1.3)	0.87	0.19
Patients with ≥1 event (%)	63	60			
Use of rescue medications					
No. of events	248	241			
No. of events/person-yr	3.0	2.8	0.9 (0.7–1.3)	0.62	0.05
Patients with ≥1 event (%)	46	45			
Night awakening					
No. of events	2518	2409			
No. of events/person-yr	30	28	0.9 (0.6–1.4)	0.70	0.31
Patients with ≥1 event (%)	55	52			

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# Change in Secondary Outcomes from Baseline to 24 Weeks.

Table 4. Change in Secondary Outcomes from Baseline to 24 Weeks.*					
Variable	Mean Change from Baseline to 24 Weeks (95% CI)		Treatment Effect (95% CI)	P Value	
	Placebo	Esomeprazole		Esomeprazole vs. Placebo†	Gastro-esophageal Reflux Interaction‡
Pulmonary function					
Prebronchodilator FEV <sub>1</sub> (liters)	−0.02 (−0.06 to 0.01)	0.00 (−0.04 to 0.04)	0.03 (−0.03 to 0.08)	0.36	0.55
Prebronchodilator FVC (liters)	−0.03 (−0.06 to 0.01)	0.00 (−0.04 to 0.05)	0.03 (−0.03 to 0.09)	0.30	0.77
Postbronchodilator FEV <sub>1</sub> (% change from prebronchodilator value)	−0.4 (−1.6 to 0.9)	−1.3 (−3.4 to 0.7)	−1.0 (−3.4 to 1.1)	0.43	0.38
Peak flow rate (liters/min)	3.2 (−3.5 to 9.9)	9.2 (1.8 to 16.6)	6.0 (−3.9 to 15.0)	0.24	0.03
PC <sub>20</sub> (mg/ml)§	1.5 (0.2 to 2.9)	0.3 (−1.4 to 0.9)	−1.1 (−3.6 to −0.1)	0.04	0.68
Asthma scores¶					
JACQ	−0.3 (−0.4 to −0.2)	−0.2 (−0.3 to −0.1)	0.1 (0.0 to 0.2)	0.11	0.73
ASUI	0.05 (0.03 to 0.07)	0.02 (0.01 to 0.04)	−0.02 (−0.05 to −0.02)	0.11	0.75
MiniAQLQ	0.3 (0.2 to 0.4)	0.3 (0.2 to 0.4)	−0.1 (−0.2 to 0.1)	0.33	0.81
SF-36 score					
Physical component	2.0 (1.1 to 2.9)	1.1 (0.3 to 1.9)	−0.9 (−2.0 to 0.4)	0.16	0.58
Mental component	0.0 (−1.8 to 1.1)	0.4 (−0.5 to 1.4)	0.5 (−1.1 to 2.0)	0.56	0.46
Gastric symptoms					
GSAS score**	−0.17 (−0.21 to −0.12)	−0.16 (−0.20 to −0.11)	0.01 (−0.05 to 0.07)	0.76	0.99
No. of symptoms	−1.7 (−2.1 to −1.3)	−1.9 (−2.3 to −1.6)	−0.2 (−0.8 to 0.3)	0.39	0.39

# GERD and Asthma

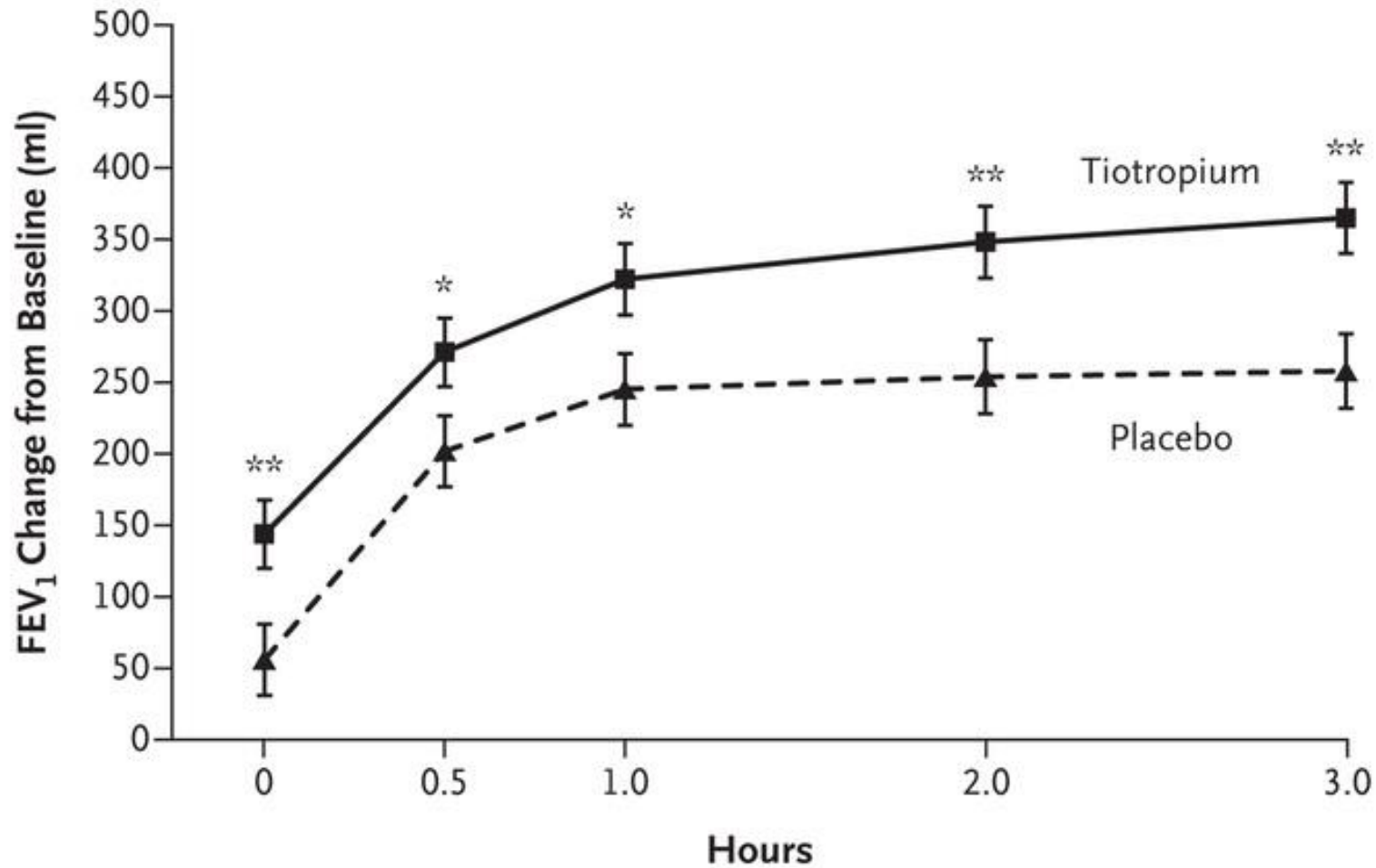
- 40% of asthma subjects had significant GERD on esophageal pH probe
- Treating it did not improve asthma control
- No empiric GERD therapy in asthma patients who may have asymptomatic GERD
- No evidence for esophageal pH monitoring to detect (and treat) asymptomatic GERD in asthma patients

# Tiotropium and asthma

- Inadequately controlled asthma
  - chronic obstruction on PFTs
  - at least 1 exacerbation in prior year
- **Already on LABA-ICS combination**
- Randomize to addition of tiotropium (LAMA) or placebo
- 912 patients (from two parallel trials)
- Primary endpoints:
  - FEV1 changes
  - time to first severe asthma exacerbation

# Lung Function and Severe Exacerbations.

A FEV<sub>1</sub> Change in Trial 1

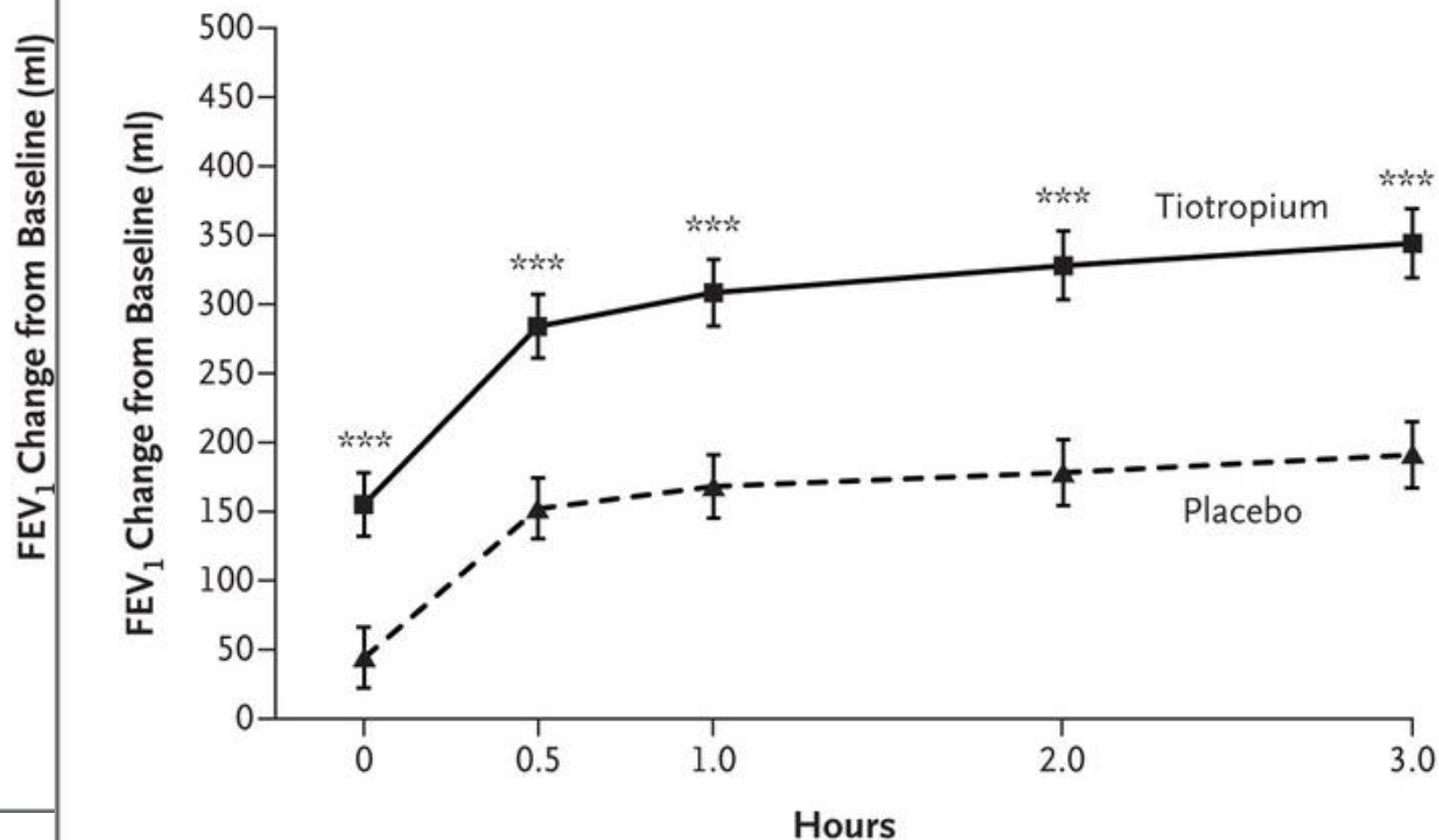




# Lung Function and Severe Exacerbations.

A FEV<sub>1</sub> Change in Trial 1

B FEV<sub>1</sub> Change in Trial 2



# Lung Function and Severe Exacerbations.

**A** FEV<sub>1</sub> C

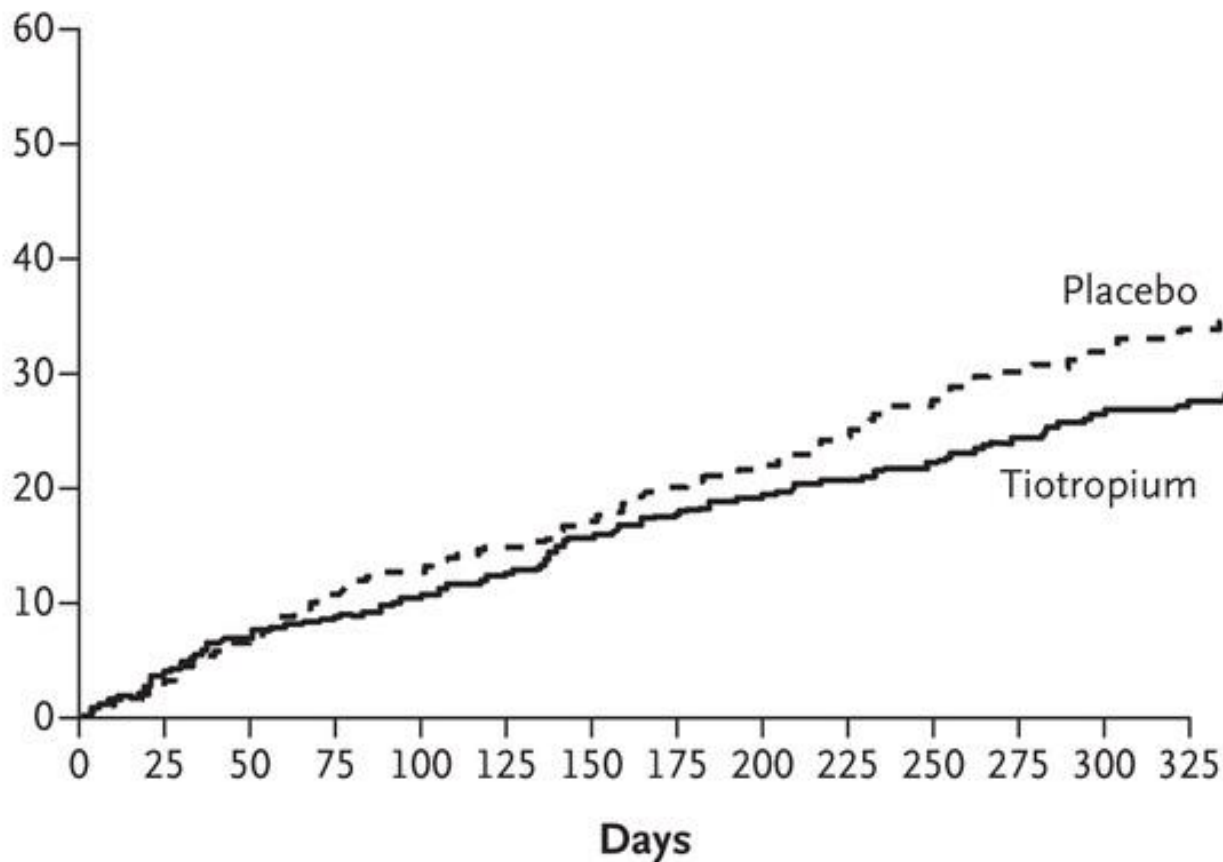
FEV<sub>1</sub> Change from Baseline (ml)

**B**

FEV<sub>1</sub> Change from Baseline (ml)

**C** Severe Exacerbation

Patients with at Least One Severe Asthma Exacerbation (%)



**No. at Risk**

Placebo

454 435 412 338 379 367 356 339 332 319 303 290 282 272

Tiotropium

453 430 409 401 389 378 363 353 348 339 331 319 308 298

LABA and concern for  
increased mortality in  
asthma patients

# SMART study

- Salmeterol vs. placebo
- 28 weeks
- Asthma

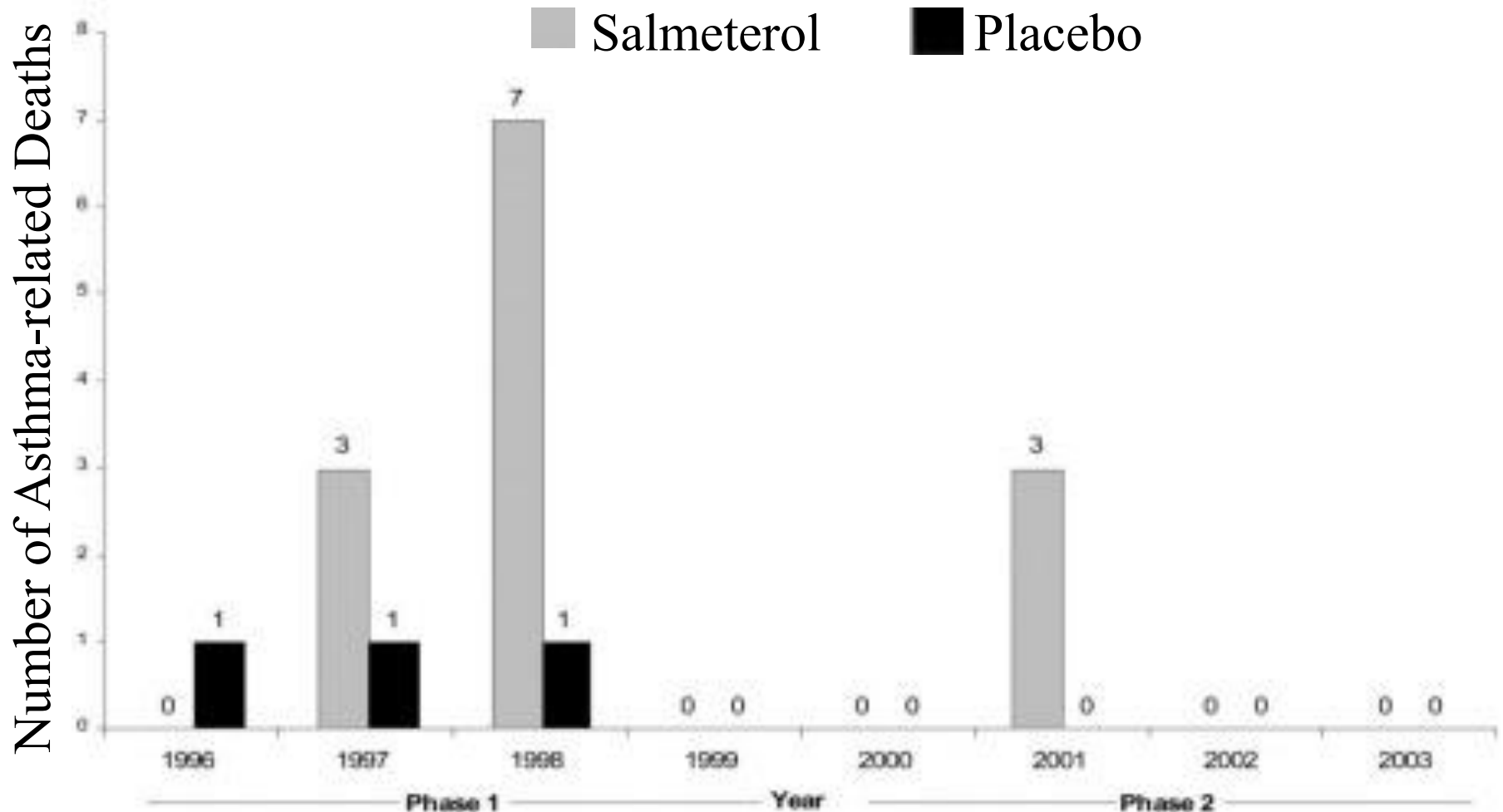
# Does LABA therapy increase mortality in asthma?



# SMART study

- Following an interim analysis in 26,355 subjects, the study was terminated due to findings in African Americans and difficulties in enrollment.
- The occurrence of the primary outcome, respiratory-related deaths, or life-threatening experiences was low and not significantly different for salmeterol vs placebo (50 vs 36; relative risk [RR] = 1.40; 95% confidence interval [CI], 0.91 to 2.14).
- There was a small, significant increase in respiratory-related deaths (24 vs 11; RR, 2.16; 95% CI, 1.06 to 4.41) and asthma-related deaths (13 vs 3; RR, 4.37; 95% CI, 1.25 to 15.34), and in combined asthma-related deaths or life-threatening experiences (37 vs 22; RR, 1.71; 95% CI, 1.01 to 2.89) in subjects receiving salmeterol vs placebo.

# Increased mortality in asthma with LABA?



# SMART study: subgroup analyses

- The imbalance occurred largely in the African-American subpopulation:
- respiratory-related deaths or life-threatening experiences salmeterol vs. placebo (20 vs 5; RR, 4.10; 95% CI, 1.54 to 10.90)
- combined asthma-related deaths or life-threatening experiences salmeterol vs. placebo (19 vs 4; RR, 4.92; 95% CI, 1.68 to 14.45)
- Whether this risk is due to factors including but not limited to a physiologic treatment effect, genetic factors, or patient behaviors leading to poor outcomes remains unknown.

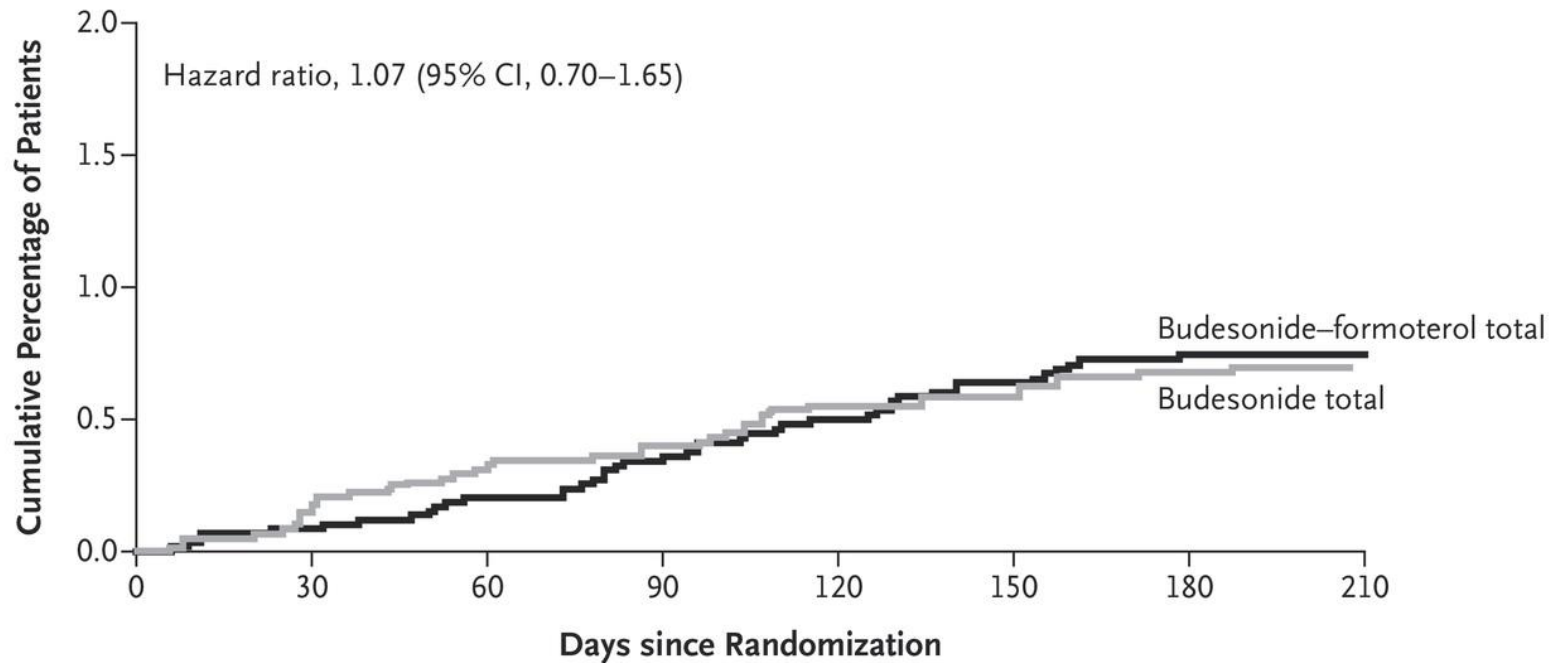


# Does LABA-ICS increase mortality compared with ICS alone in asthma?

- 26 week prospective, double-blind, multicenter RCT
- ICS vs. LABA-ICS
- Age 12 and older; 1-4 exacerbations in prior year
- primary end point: first serious asthma-related event
  - (a composite of adjudicated death, intubation, and hospitalization)
  - as assessed in a time-to-event analysis.
- 11,693 patients randomized

# Time-to-Event Analysis of the Risk of a First Serious Asthma-Related Event and the Risk of a First Asthma Exacerbation.

## A Time to First Serious Asthma-Related Event



### No. at Risk

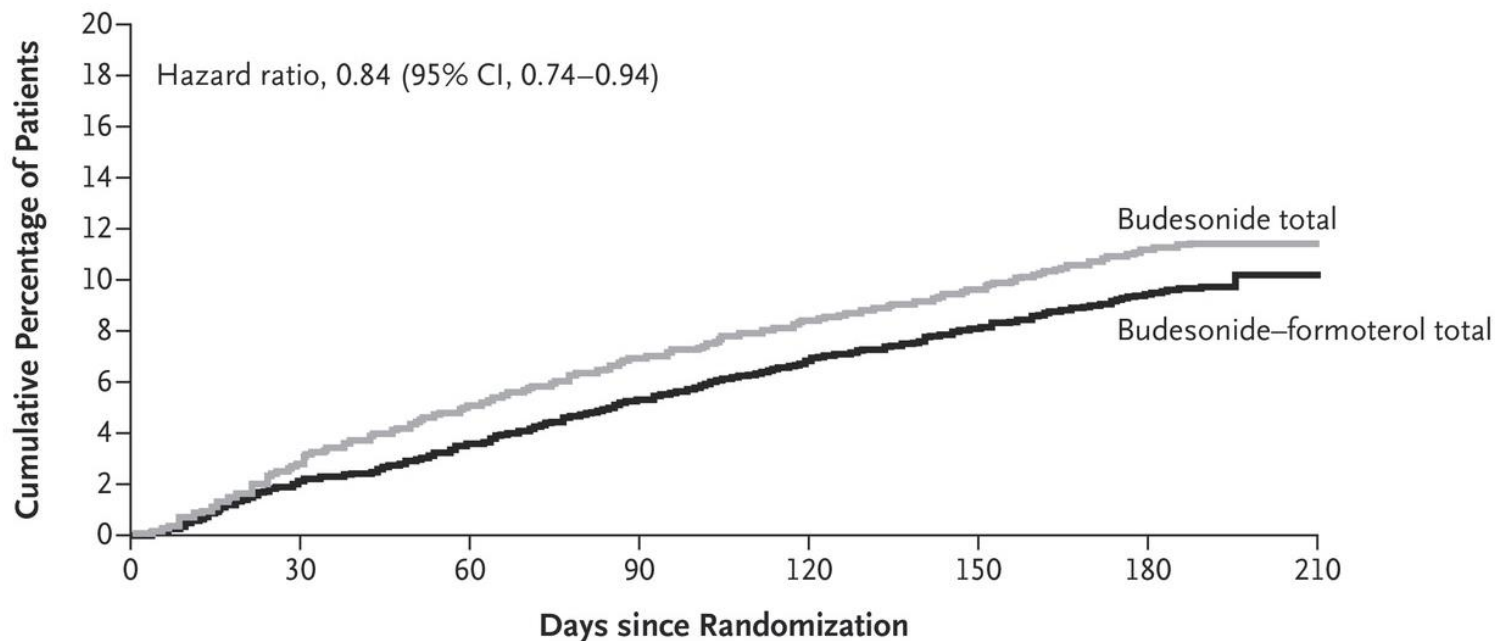
Budesonide-formoterol	5846	5814	5783	5753	5737	5722	5704	44
Budesonide	5847	5799	5773	5745	5720	5701	5676	33

# Time-to-Event Analysis of the Risk of a First Serious Asthma-Related Event and the Risk of a First Asthma Exacerbation.

## A Time to First Serious Asthma-Related Event

ts 2.0

## B Time to First Asthma Exacerbation



### No. at Risk

Budesonide-formoterol	5846	5589	5406	5257	5117	5011	4863	38
Budesonide	5847	5532	5321	5116	4972	4848	4715	27

38 yo M w/ asthma, poorly controlled, daily symptoms, using daily inhaled steroid and prn albuterol 3-5 times a day w/ frequent early am awakenings due to wheezing. Which do you recommend next?

1. Add LAMA (e.g. tiotropium)
2. Add ICS-LABA combination (e.g. budesonide-formoterol)
3. Add omeprazole
4. Start PO prednisone for a month and then wean as tolerated
5. Azithromycin x 5 days

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**2. Add ICS-LABA combination (e.g. budesonide-formoterol)**

3. Add omeprazole

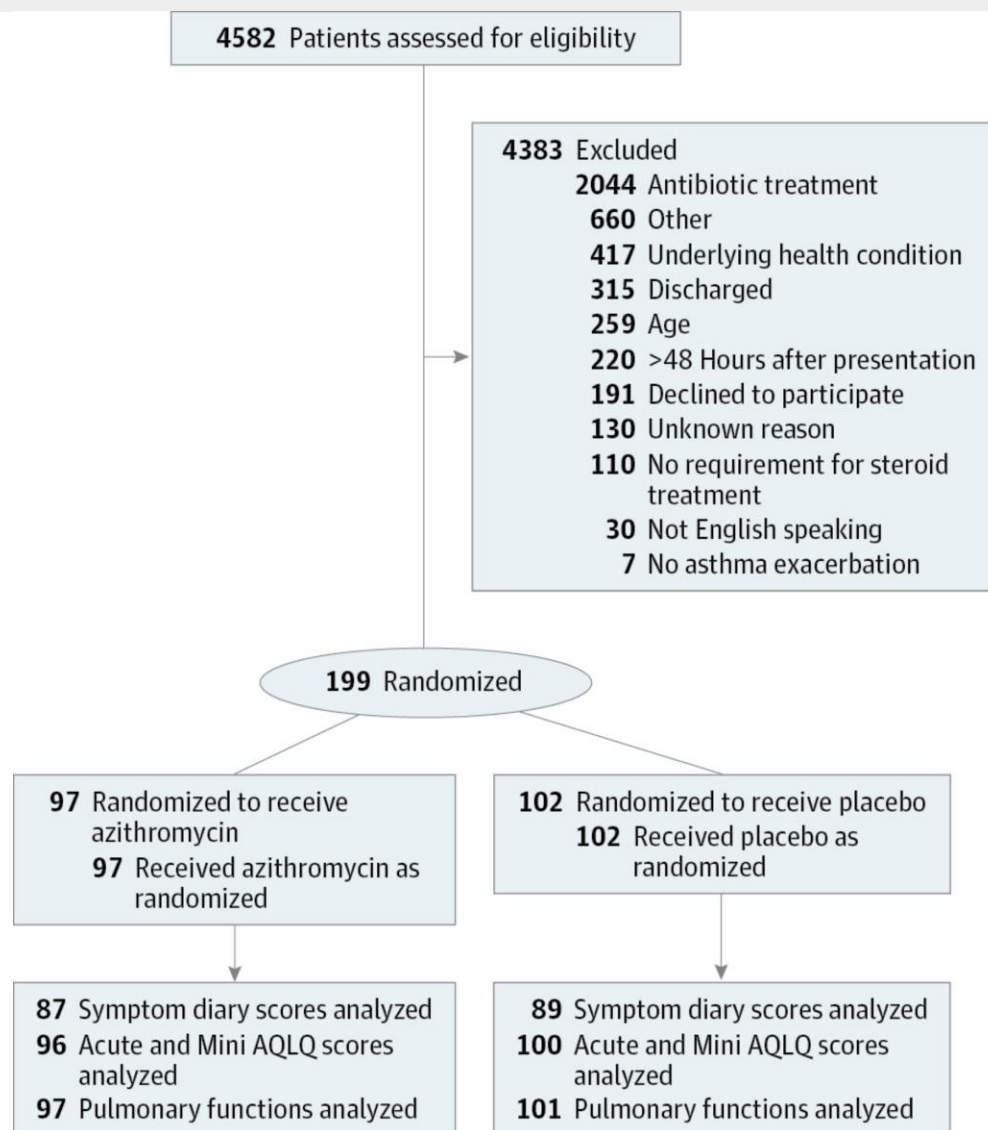
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5. Azithromycin x 5 days

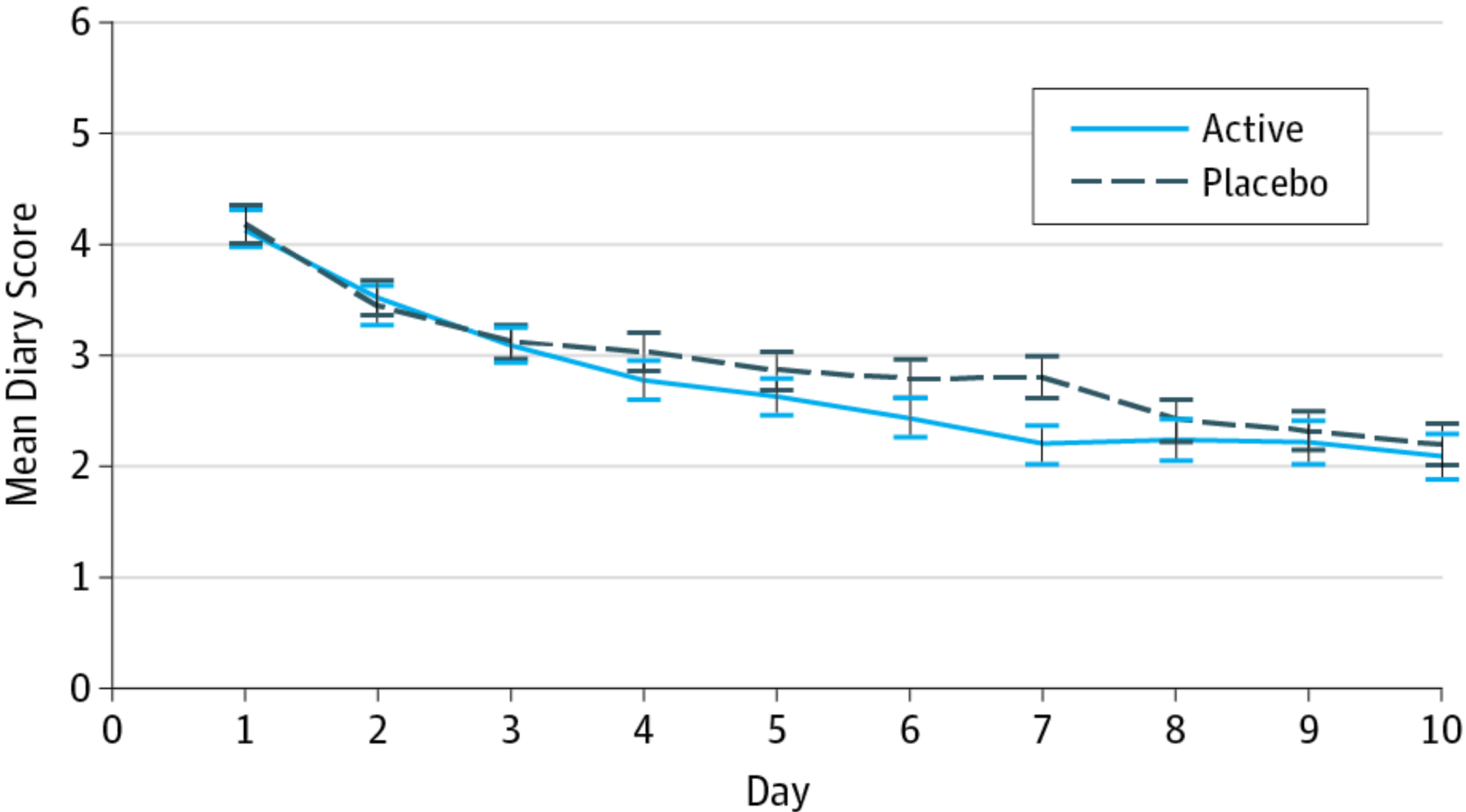
45 yo W w/ hx asthma on ICS-LABA developed rhinorrhea, cough and wheezing x 3 days. She is missing work and is unable to sleep because of her symptoms. Her husband, and daughter also had similar symptoms a week earlier that have now resolved. What would you recommend?

1. Add LAMA (e.g. tiotropium) to her regimen
2. Azithromycin 500mg po qday x 3 days
3. Doxycycline 100mg po BID x 7 days
4. Levofloxacin 750mg po qday x 7 days
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6. Oseltamivir (tamiflu) 75mg po BID x 5 days

# Azithromycin for Acute Exacerbations of Asthma

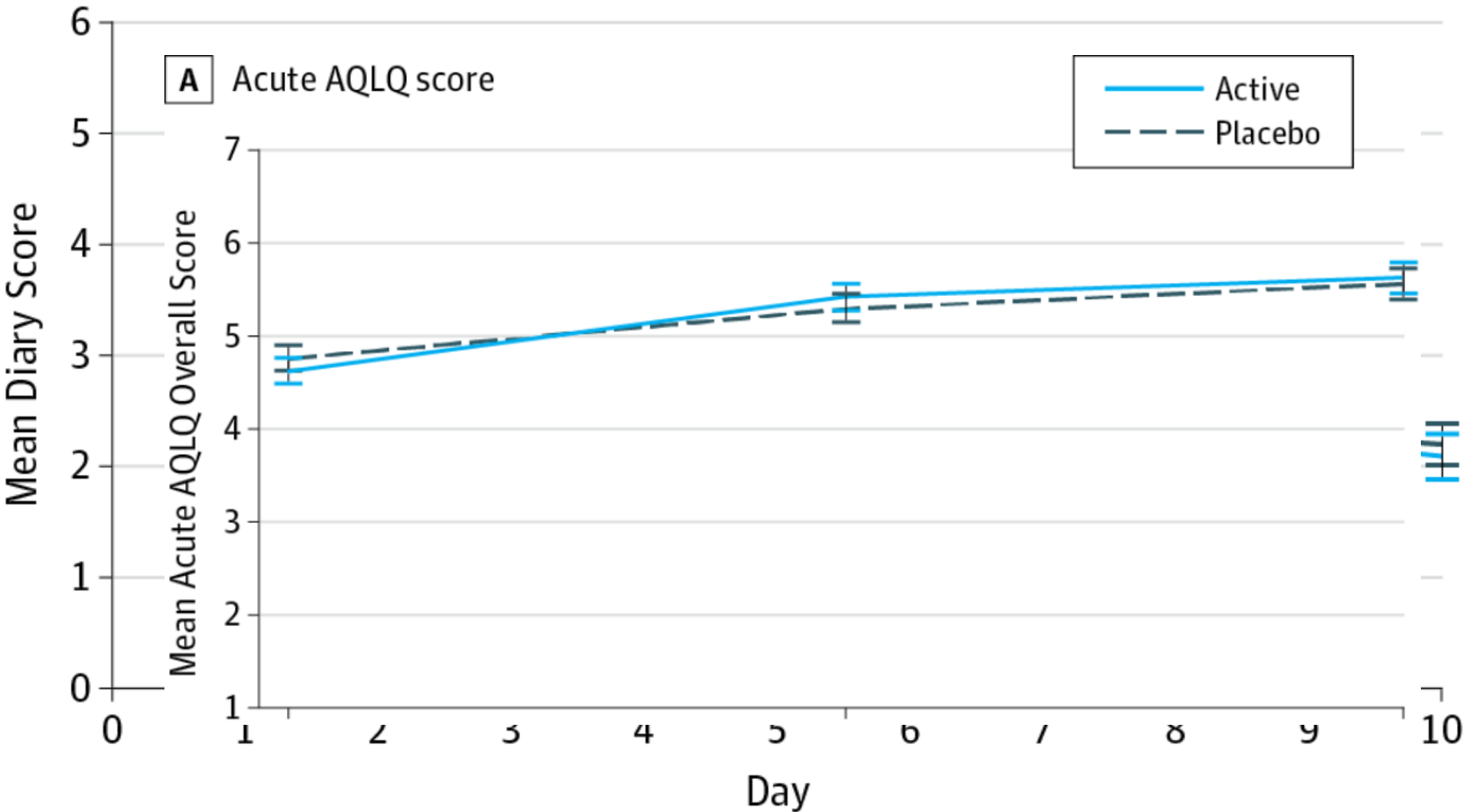


# Azithromycin for Acute Exacerbations of Asthma

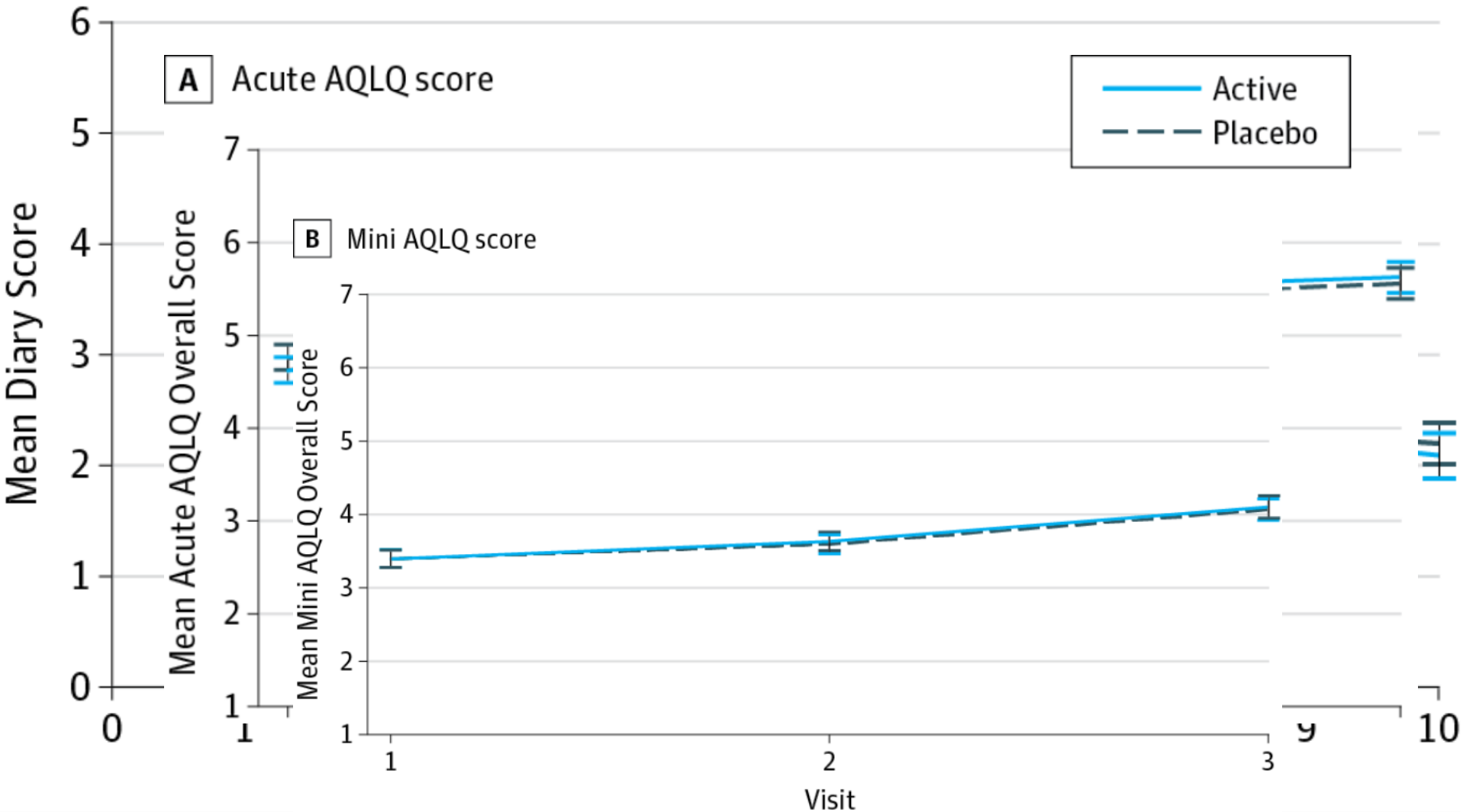




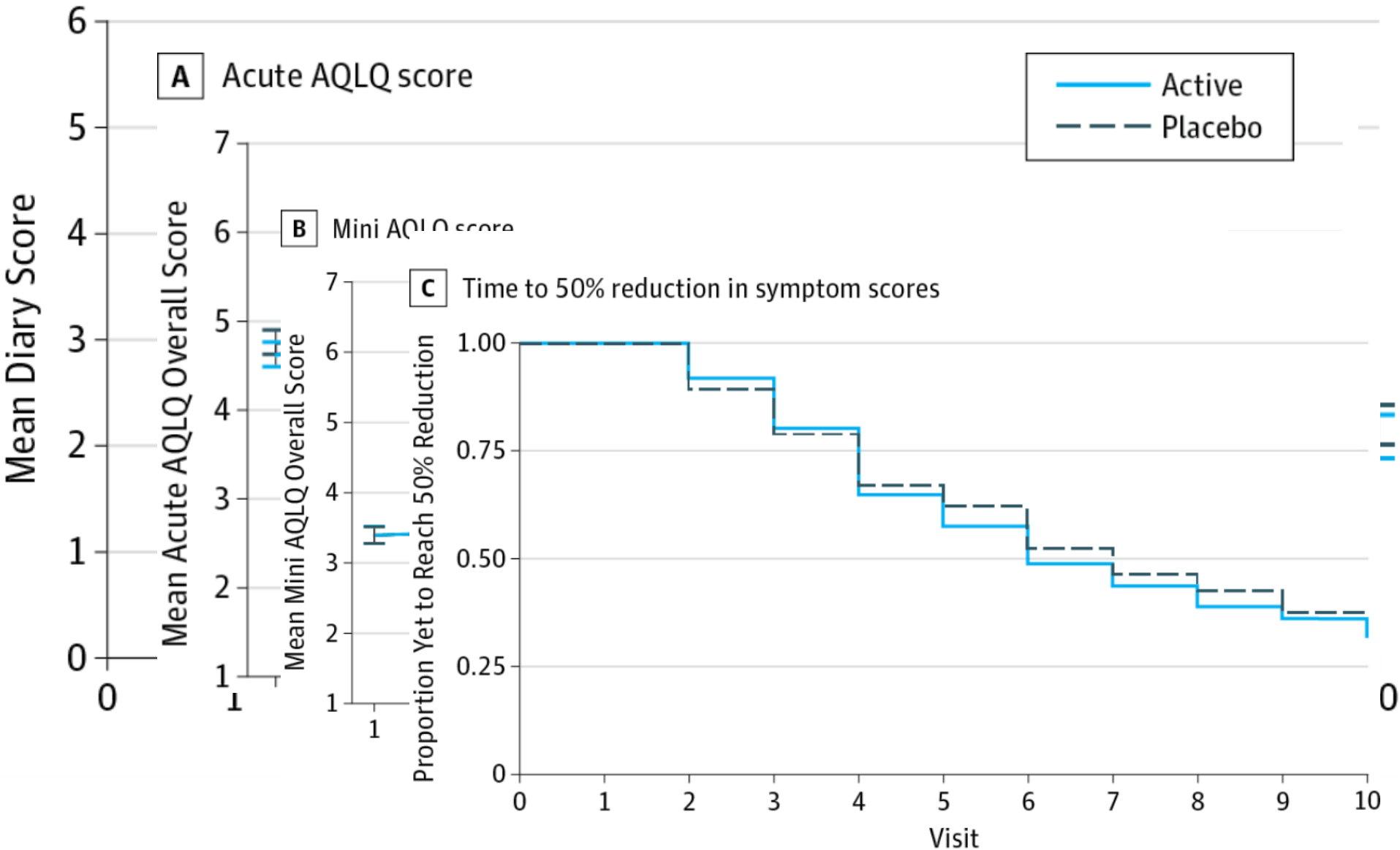
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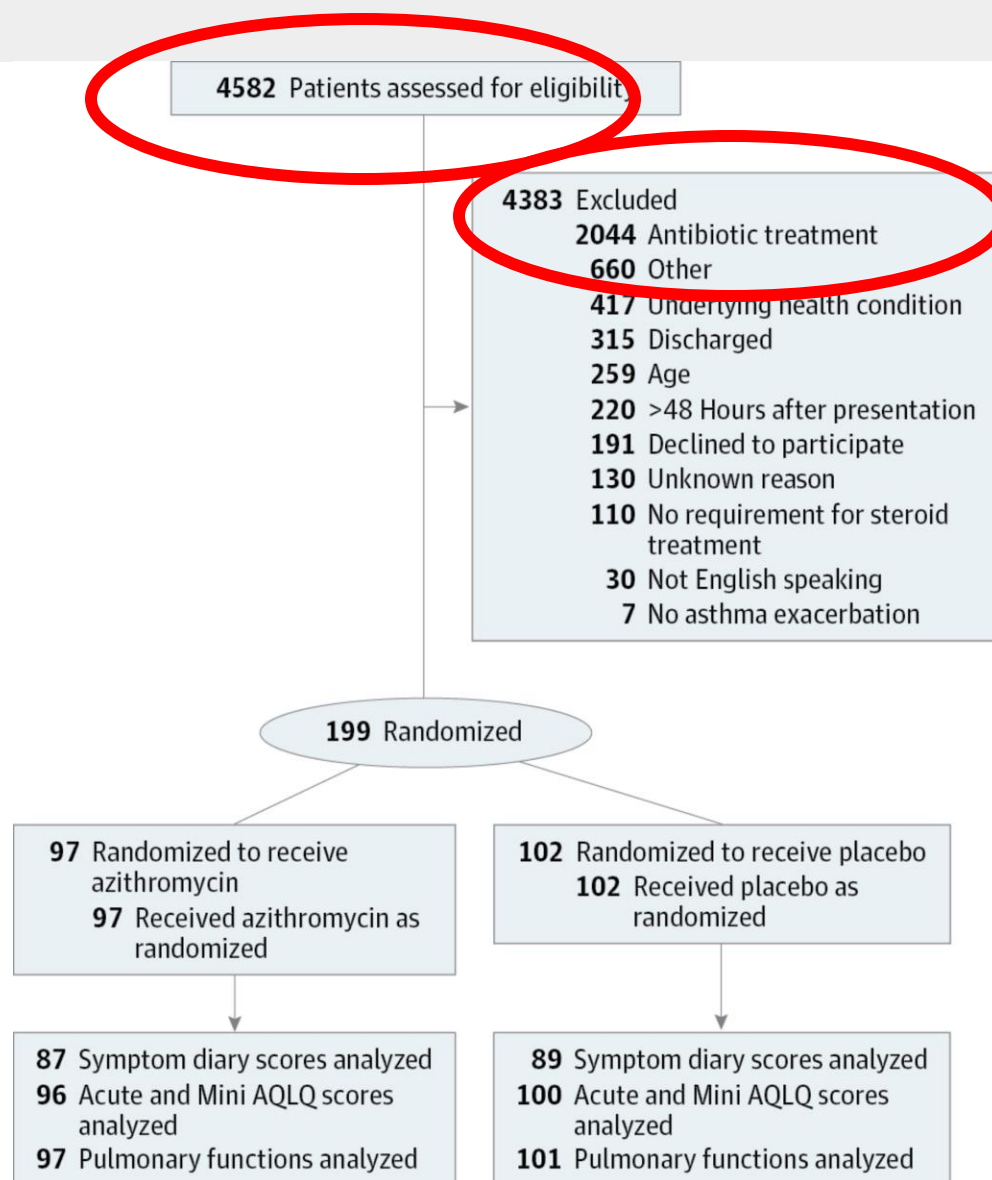
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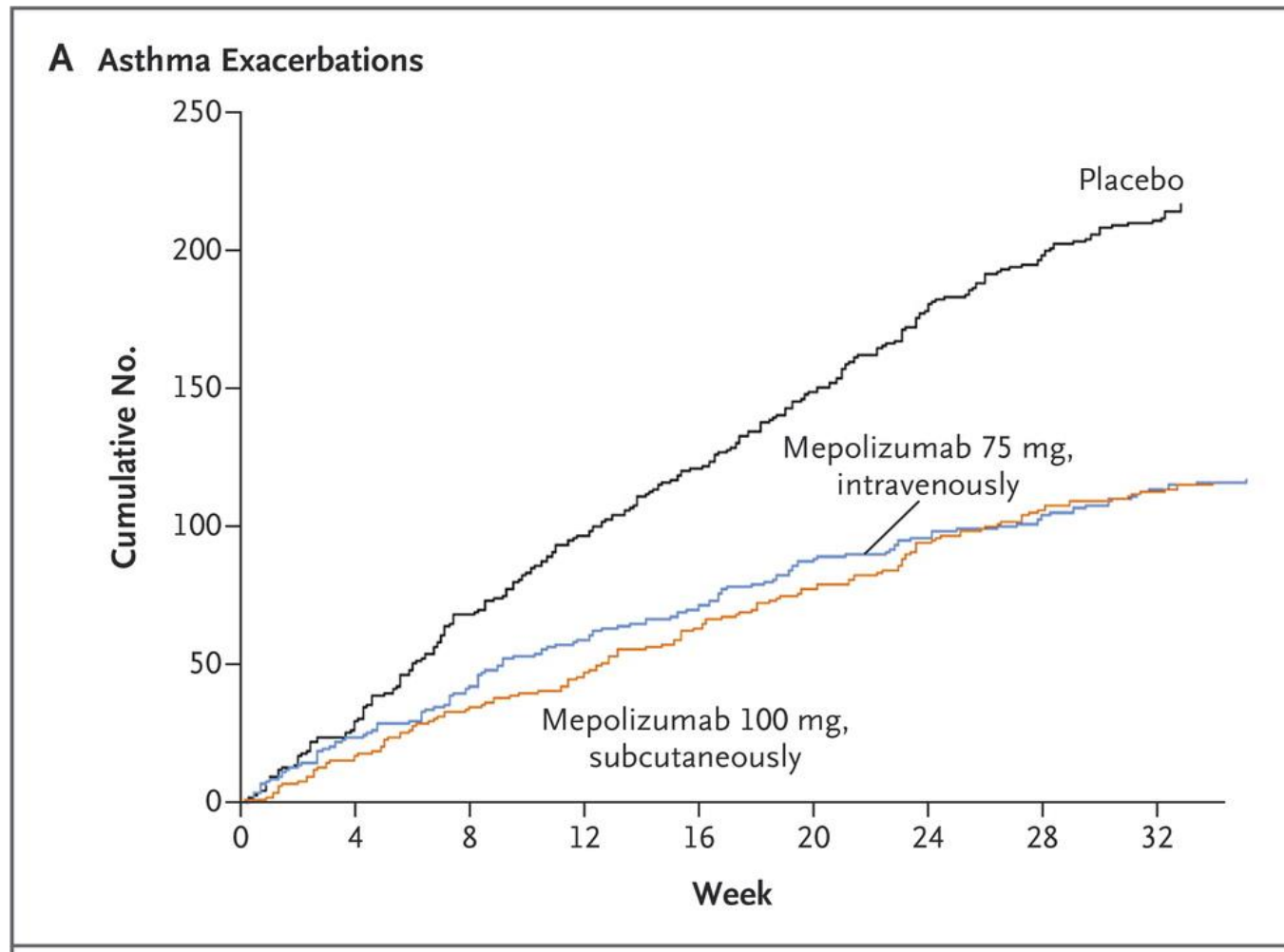
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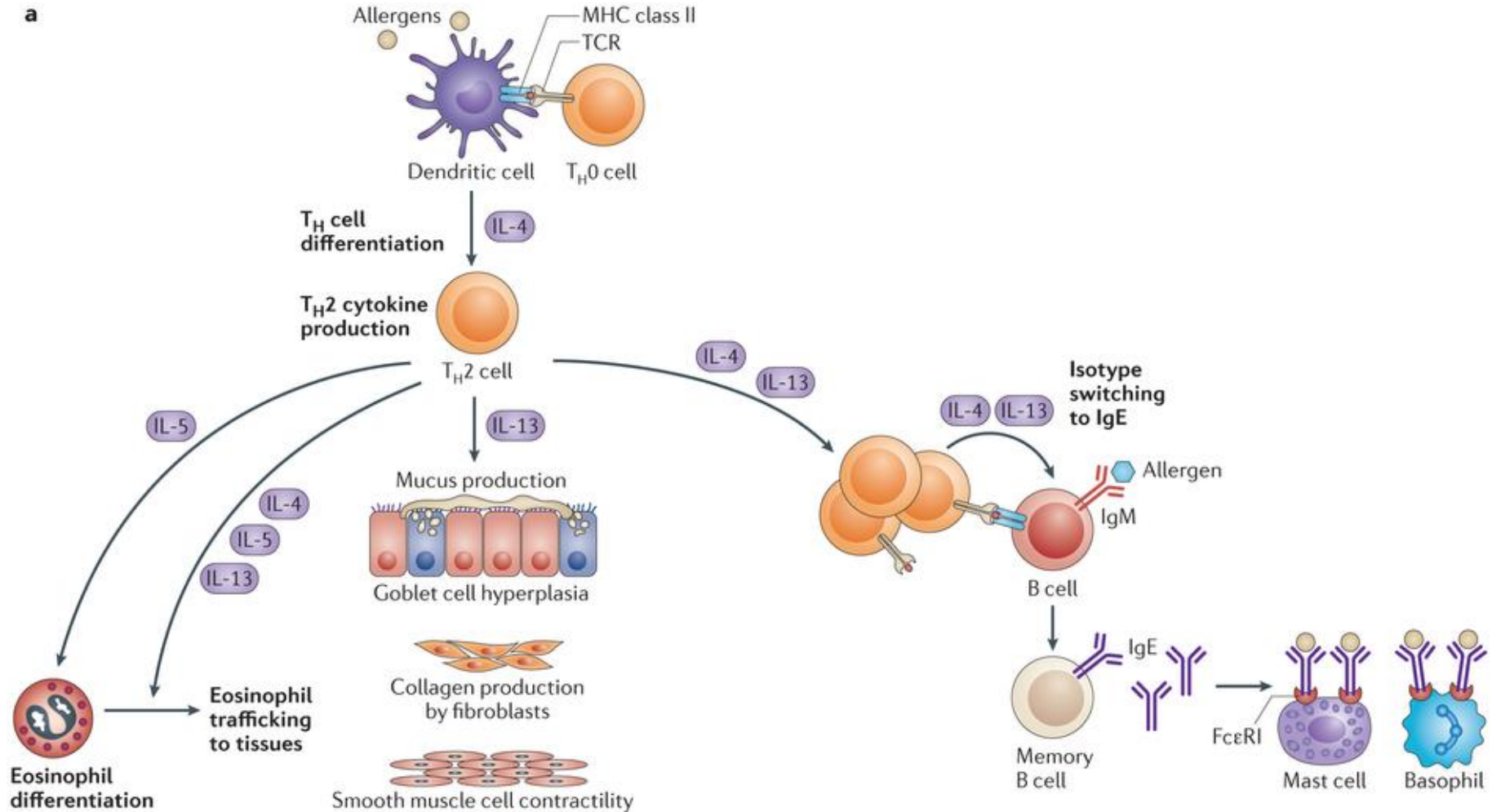
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# Asthma Exacerbations: Mepolizumab



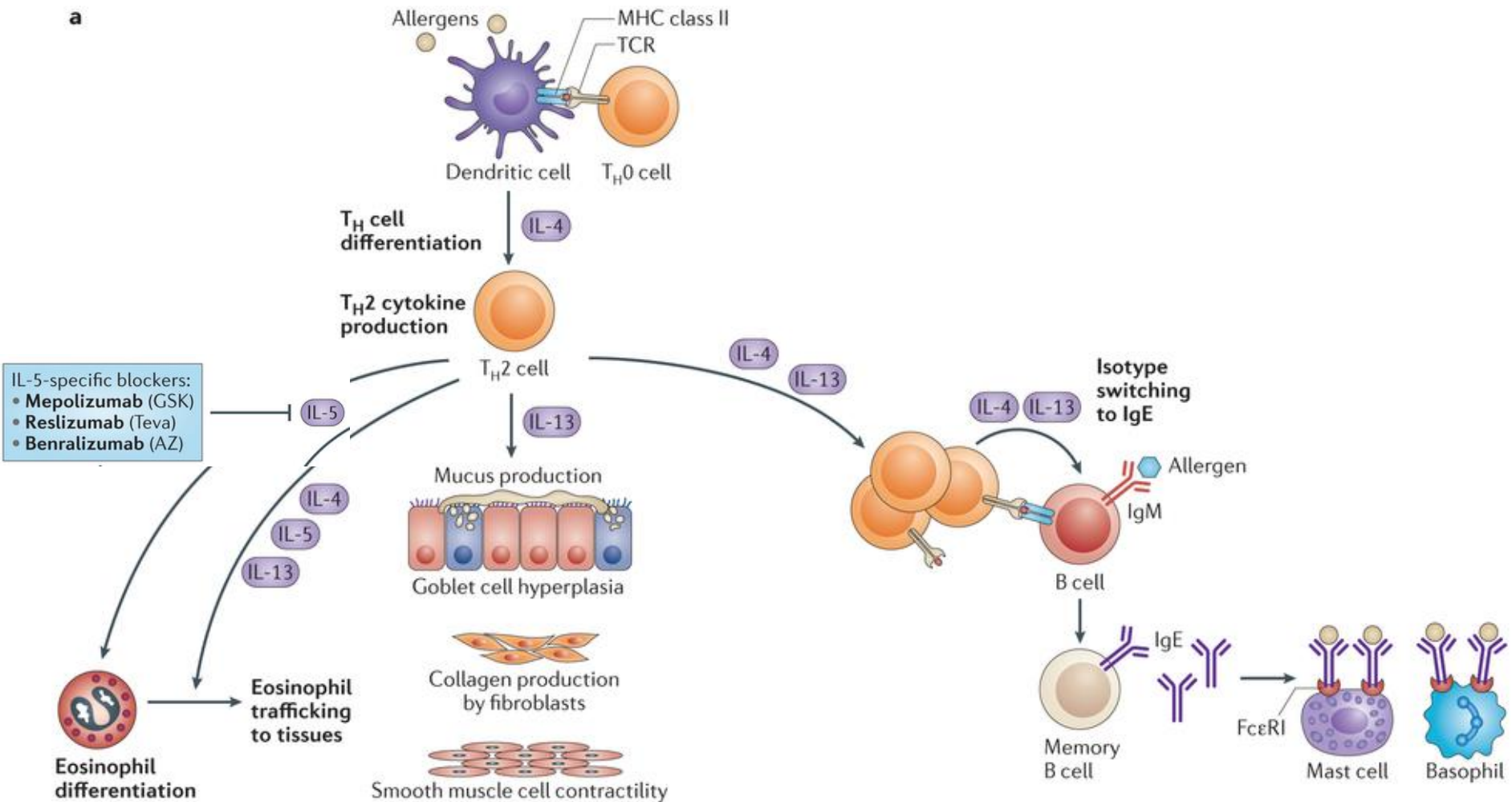
Ortega HG et al. N Engl J Med 2014;371:1198-1207.

# Asthma and allergic disease

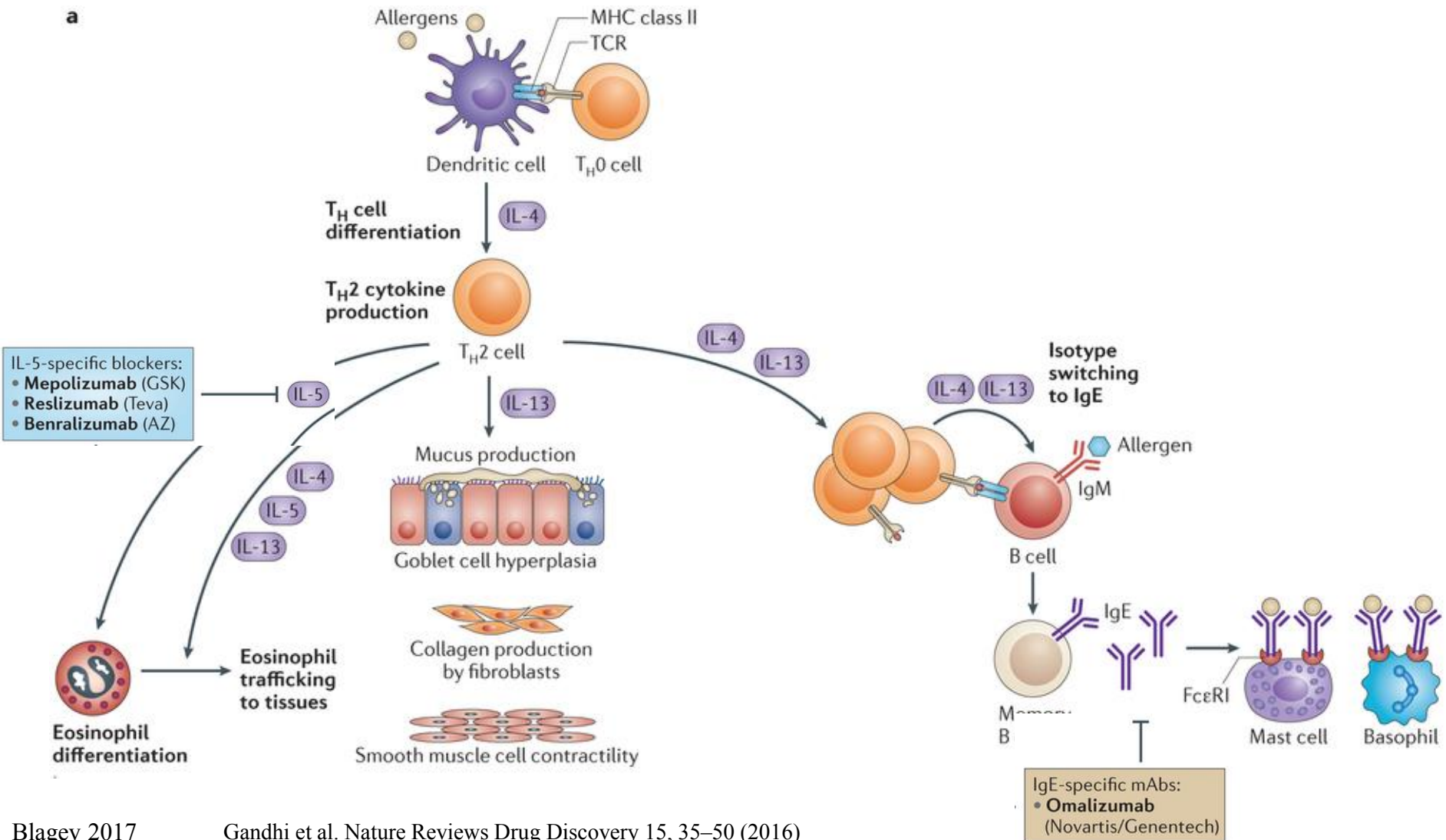




# “TH2” inflammation type asthma



# “TH2” inflammation type asthma



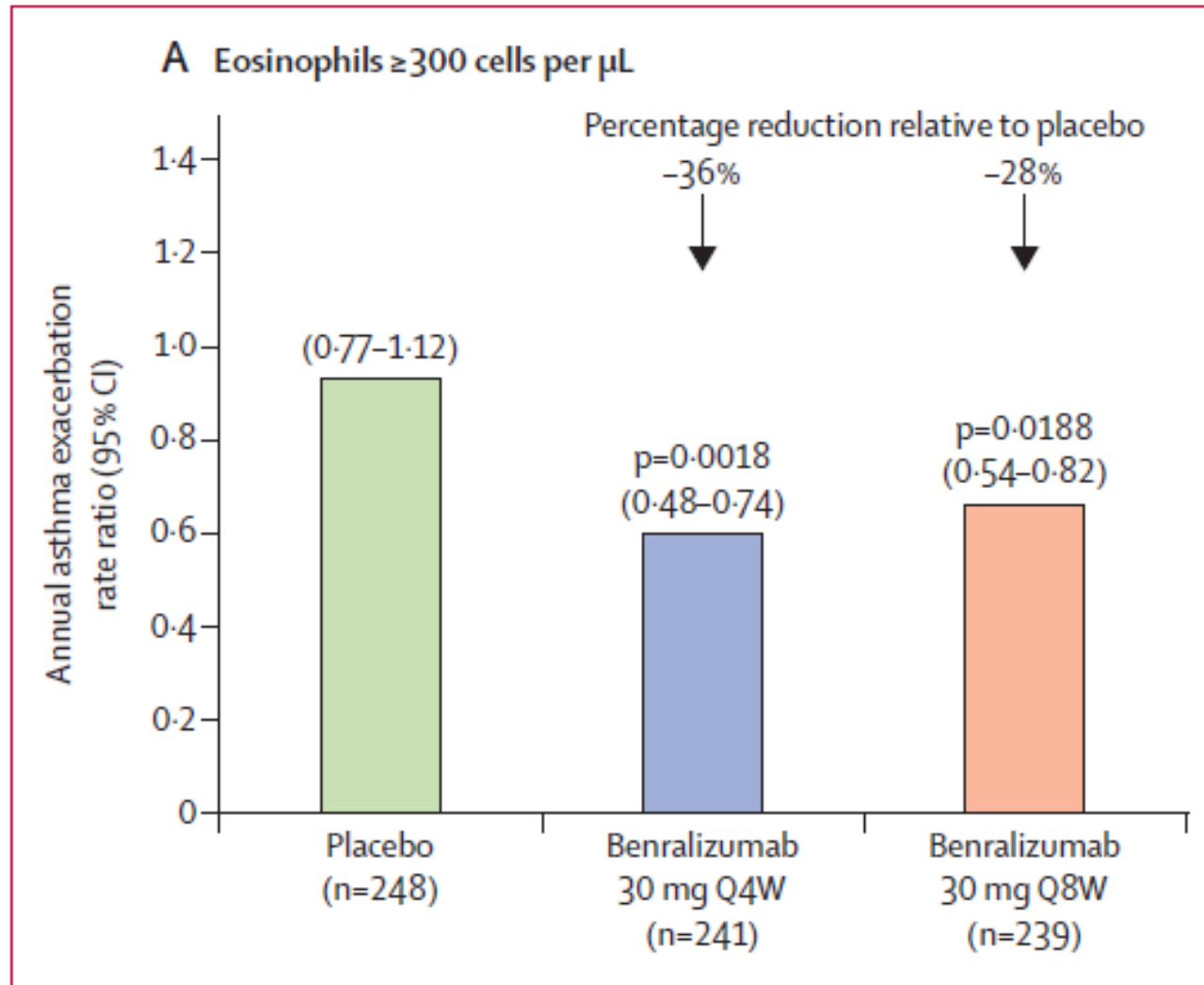
# Anti-IL-5 therapies

- High risk severe asthma (PFT abnormalities)
- Already on therapy (ICS and LABA/controller)
  - Significant portion of patients are on oral steroids
- 2 or more exacerbations/year
- Peripheral eosinophilia (abs 300 or greater)
- Kids and adults (12-75/80's)

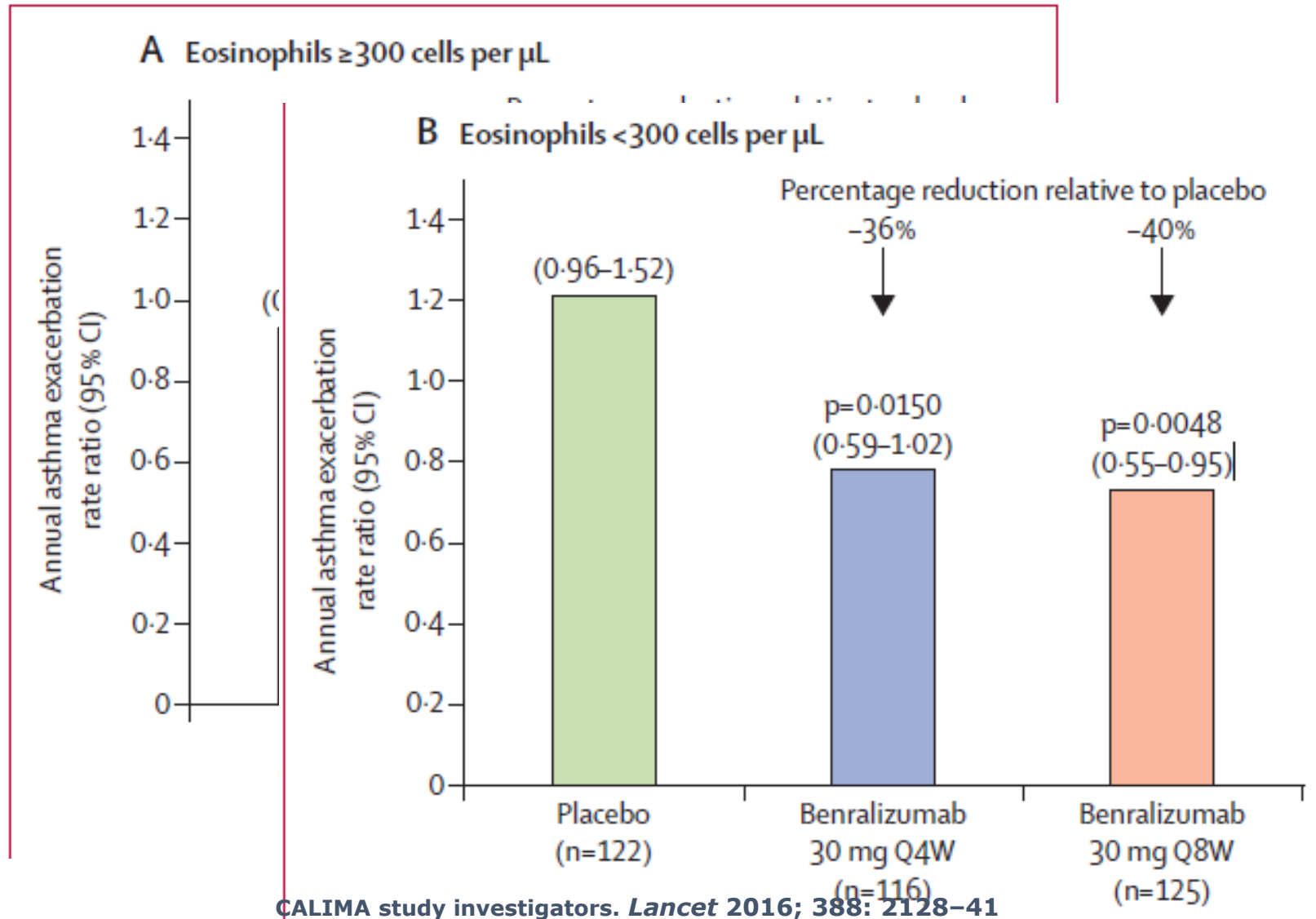
# Severe Eosinophilic Asthma – new treatment options

- 1,306 patients - Age 12-75
- ICS and LABA
- 2 or more exacerbations/year
- Randomized to anti-IL-5 Q4W, anti-IL-5 Q8W, and placebo;
- stratified by blood eos 300 or greater ug/ml
- OUTCOME: annual exacerbation rate

# Reduced asthma exacerbations



# Reduced asthma exacerbations



# Adverse effects

	Placebo (n=440)	Benralizumab 30 mg Q4W (n=438)	Benralizumab 30 mg Q8W (n=428)
Any adverse event	342 (78%)	322 (74%)	320 (75%)
Any drug-related adverse event	36 (8%)	51 (12%)	54 (13%)
Any adverse event leading to treatment discontinuation	4 (<1%)	8 (2%)	10 (2%)
Any adverse event leading to death	0	2 (<1%)	2 (<1%)
Any serious adverse event	60 (14%)	45 (10%)	40 (9%)
Adverse event in >3% of patients*			
Nasopharyngitis	92 (21%)	90 (21%)	79 (18%)
Asthma	68 (15%)	61 (14%)	47 (11%)
Bronchitis	52 (12%)	40 (9%)	44 (10%)
Upper respiratory tract infection	41 (9%)	29 (7%)	36 (8%)

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43 yo M w/ hx severe asthma has been hospitalized for asthma twice in the last year. He is currently on montelukast controller with albuterol as needed, which he uses three times a day. Which of the following is the next step in asthma therapy?

1. Bronchial Thermoplasty
2. Mepolizumab (Anti-IL-5)
3. Benralizumab (Anti IL-5 Ab)
4. Omalizumab (Anti IgE)
5. Add ICS/LABA combination

43 yo M w/ hx severe asthma has been hospitalized for asthma twice in the last year. He is currently on montelukast controller with albuterol as needed, which he uses three times a day. Which of the following is the next step in asthma therapy?

1. Bronchial Thermoplasty
2. Mepolizumab (Anti-IL-5)
3. Benralizumab (Anti IL-5 Ab)
4. Omalizumab (Anti IgE)
- 5. Add ICS/LABA combination**
- 6. Trigger evaluation? Correct diagnosis?**

Questions?



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**2 MINUTE  
TIME LIMIT**

**IT'S OUR HEALTH, AND THE LAW.**

# “TH2” inflammation type asthma

